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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/843,819	04/30/2001	Tomoko Nakayama	P107424-00027	9941

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/843,819	Applicant(s) NAKAYAMA ET AL.	
	Examiner Sally A Sakelaris	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 2/24/2004. Claims 1-3 have been amended, claim 12 has been canceled, and no claims have been added. Claims 1-11 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1, 3-9 and 11, are rejected under U.S.C. 103(a) as being unpatentable

over Ivanov et al. (US Patent 6,183,998 filed October 31st 1998).

Ivanov et al. teach a method for synthesis of nucleic acids to amplify an intended nucleic acid region in which a content of guanine (G) and cytosine (C) is rich, wherein an aliphatic polyhydric alcohol, glycerine(aka glycerol) is present in an amplification reaction solution as well as a reaction with ammonium sulfate, wherein a cellular or intracellular level body comprising nucleic acids from a living body-derived sample itself or the living body-derived sample itself is added to the amplification reaction solution. Ivanov et al. teach "PCR reactions may be improved by using additives that affect the melting behavior of nucleic acids in the reaction mixture. For example, difficult PCR amplification, such as reaction that yield non-specific products, and especially amplification of templates having a high GC content or having extensive secondary structure, may be improved by employing additives that 'isostabilize' AT- and GC-base pairing to the level of AT-base pair stability."(Column 8 lines 11-18). The reference goes on to teach that suitable additives that can be used to this end of amplifying high GC content sequences include "most preferably glycerol" and also "most preferably ammonium sulfate"(Col. 8 lines 20 and 25). Ivanov et al. do not specifically exemplify as a single embodiment a method in which the synthesis of nucleic acids is performed in the presence of both glycerol and ammonium sulfate. However, in view of the fact that Ivanov teaches that amplification reactions should be performed in the presence of additives such as glycerol or ammonium sulfate, it would have been obvious to one of ordinary skill in the art at the time the invention was made to performed the amplification method of Ivanov using a reaction mixture that contained both glycerol and ammonium sulfate in order to have achieved the expected benefit expressly stated by Ivanov, of improving the specificity of the amplification method. As

discussed in MPEP 2144.06-2144.07, it is *prima facie* obvious to combine two reagents which are taught in the prior art to be useful for the same purpose and to use these reagents in combination based on their known functions. It is noted that Ivanov (column 8) teaches that "PCR reactions may be improved by using additives that affect the melting behavior of nucleic acids in the reaction mixture." And, Ivanov teaches that glycerol and ammonium sulfate are equivalents in that they both serve to "iso-stabilize" AT and GC- base pairing to the level of AT-base pairing stability.

With respect to claim 3, the reference teaches that "in order to release the primer extension activity of Taq DNA polymerase" a reaction mixture of 40 ul containing various reagents(See col. 10 lines 43-45) and "10mM Tris HCl pH 8.8 at 25 °C" was prepared(Col. 10 lines 40-47). Additionally the reference meets the alternate limitation in claim 3 through its teaching of a reaction solution that has the pH of 8.4 as it is carried through an amplification reaction that encounters an extension step at about 70°C(72 °C) as is taught in Example 8, Col. 12, lines 55-65).

With respect to claims 4 and 5, the reference teaches multiple sequences wherein the GC content in the GC rich region is both more than 40% and in the range of 50% to 70%. The reference teaches for instance the amplification of a 831bp PCR fragment of the human glycerinaldehyde-3-phosphate-dehydrogenase gene(Example 15, Col 16-18) with SEQ ID NO: 8 and 9. The resulting amplified fragment is 55% GC rich(459/831bp)(Please see attached alignments of SEQ ID NOS 8 and 9 to the human glycerinaldehyde-3-phosphate-dehydrogenase gene sequence provided).

With respect to claims 6-8, the reference teaches the above method of nucleic acid synthesis wherein the additive is a polyhydric alcohol that is an aliphatic polyhydric alcohol, glycerin(glycerol)(Col. 8 line20). Furthermore the reference teaches the method using the additive of polyethylene glycol(Col. 8 lines 26-27).

With respect to claims 9 and 11 both limitations of glycerin/glycerol being present from 2.5% to 20% by volume in the amplification solution and the second wherein ammonium sulfate is present at a concentration from 20 mM to 100 mM in the amplification reaction solution are taught in Col. 8's teaching of reaction parameters. Ivanov et al. teaches that the "PCR additives are advantageously added to a PCR reaction mixture in an amount effective to improve the specificity of the amplified product. Typically concentrations of additive from 1mM to 5M, preferably about 1M, are used, however any amount that improves the yield of the specific amplification product, compared with a PCR reaction carried out in the absence of the additive, is suitable"(Col. 8 lines 37-41).

Response to Arguments:

Applicant's arguments filed 2/24/2004 have been fully considered but they are not persuasive. Applicant asserts that their amended recitation of "a living body-derived sample itself or the living body-derived sample itself is added to the amplification reaction solution" is not taught or suggested by Ivanov et al. The phrase "intracellular level body comprising nucleic acids from a living body derived sample itself" is considered to include nucleic acids which are purified/isolated from the living body-derived sample. The term "derived" means that the material from the living body sample may be further modified in some manner. An "intracellular level body" includes genomic nucleic acids, and is not limited to, for example, an intact,

unmodified cell or an intact, unmodified cellular organelle. Further, it is noted that the specification at page 4 states that "the term 'itself' means that no special pretreatment is required". However, this recitation does not specifically exclude pretreatment. Rather, the recitation indicates that it is not essential to pretreat the sample. Thereby, these teachings in the specification indicate that pretreatment may occur, but it is not essential. Accordingly, it is maintained that the claims as written are inclusive of methods of adding nucleic acids to the amplification reaction containing glycerol and ammonium sulfate, as is taught in the method of Ivanov.

2. Claim 10 is rejected under U.S.C. 103(a) as being unpatentable over Ivanov et al. (US Patent 6,183,998) in view of Yamada et al. or Kelly et al. or Holliger et al. or Ukachi et al. or Endo et al. or Taniguchi et al. (respectively US Patents 5,369,096; 4,978,757; 4,820,309; 4,683,280; 4,368,314; 6,054501).

The teachings of Ivanov et al. can be reviewed from above, but do not teach the limitation of claim 10 wherein the additive is ethylene glycol.

However, Yamada et al., or Kelly et al., or Holliger et al., or Ukachi et al., or Endo et al., or Taniguchi et al., each teach the use of polyethylene glycol to be equivalent to that of ethylene glycol. Especially US Patent, 5,369,096, Yamada et al. teach a reaction scheme in which polyethylene glycol is used interchangeably with ethylene glycol(See Columns 7-8,compound(6)).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to replace the polyethylene glycol of Ivanov et al. with the ethylene glycol embodied in claim 10 of the present application with the expected benefit that the

chemical would function the same as the polyethylene glycol in the Ivanov et al. reference as taught by the six cited patents.

Response to Arguments:

Applicant's arguments filed 2/24/2004 have been fully considered but they are not persuasive since the only argument presented for this rejection has been addressed by the response to the above rejection in view of Ivanov et al.

-----THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS-----

3. Claim 2 is rejected under U.S.C. 103(a) as being unpatentable over Ivanov et al. (US Patent 6,183,998) in view of Sandhu et al.(US Patent 5,707,802).

Ivanov et al. teach a method for synthesis of nucleic acids to amplify an intended nucleic acid region in which a content of guanine (G) and cytosine (C) is rich, wherein an aliphatic polyhydric alcohol, glycerine(aka glycerol) is present in an amplification reaction solution as well as a reaction with ammonium sulfate, wherein a cellular or intracellular level body comprising nucleic acids from a living body-derived sample itself or the living body-derived sample itself is added to the amplification reaction solution. Ivanov et al. teach "PCR reactions may be improved by using additives that affect the melting behavior of nucleic acids in the reaction mixture. For example, difficult PCR amplification, such as reaction that yield non-specific products, and especially amplification of templates having a high GC content or having extensive secondary structure, may be improved by employing additives that 'isostabilize' AT- and GC-base pairing to the level of AT-base pair stability."(Column 8 lines 11-18). The reference goes on to teach that suitable additives that can be used to this end of amplifying high

GC content sequences include "most preferably glycerol" and also "most preferably ammonium sulfate"(Col. 8 lines 20 and 25). Ivanov et al. do not specifically exemplify as a single embodiment a method in which the synthesis of nucleic acids is performed in the presence of both glycerol and ammonium sulfate. However, in view of the fact that Ivanov teaches that amplification reactions should be performed in the presence of additives such as glycerol or ammonium sulfate, it would have been obvious to one of ordinary skill in the art at the time the invention was made to performed the amplification method of Ivanov using a reaction mixture that contained both glycerol and ammonium sulfate in order to have achieved the expected benefit expressly stated by Ivanov, of improving the specificity of the amplification method. As discussed in MPEP 2144.06-2144.07, it is *prima facie* obvious to combine two reagents which are taught in the prior art to be useful for the same purpose and to use these reagents in combination based on their known functions. It is noted that Ivanov (column 8) teaches that "PCR reactions may be improved by using additives that affect the melting behavior of nucleic acids in the reaction mixture." And, Ivanov teaches that glycerol and ammonium sulfate are equivalents in that they both serve to "iso-stabilize" AT and GC- base pairing to the level of AT-base pairing stability.

With respect to claim 2, the reference teaches the above method of synthesis of nucleic acids wherein the nucleic acids to be amplified, come from a cellular or intracellular level body comprising nucleic acids from a living body-derived sample itself such as cells from a HeLa human cell line in example 15,(Col. 17) or from a living body derived sample itself such as human blood as taught in examples 7 and 8(Col. 11 and 12 respectively).

Ivanov et al. do not teach the method of claim 1 wherein the cellular or intracellular level

body comprising nucleic acids is a cell, fungus, bacterium, or virus that is added directly to the amplification reaction solution.

However, Sandhu et al. teach performing PCR directly on a fungal culture. The reference in Col. 6 lines 56-67, teaches that "a loopful of fungal culture was scraped off a culture plate using a sterile inoculation loop. The fungus was added [to] one milliliter of sterile water in a 1.5 ml Sarsted screw cap microcentrifuge tube. This tube was placed in a boiling water bath for 20 minutes in order to lyse the fungus and release DNA from the cells. Two microliters of this whole cell lysate was used in a PCR to amplify 28S rDNA". The reference later teaches the inclusion of 50% glycerol in the PCR reaction in Col. 7 line 10 of the patent.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have directly added a whole cell lysate to the glycerol containing amplification reaction of Sanhu et al and further to have added ammonium sulfate as taught by the Ivanov reference since "PCR reactions may be improved by using additives that affect the melting behavior of nucleic acids in the reaction mixture."(Col. 8) And, further that the addition of ammonium sulfate would prove helpful in PCR since Ivanov teaches that glycerol and ammonium sulfate are equivalents in that they both serve to "iso-stabilize" AT and GC- base pairing to the level of AT-base pairing stability.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-11 are indefinite over the recitation of "cellular or intracellular level body comprising nucleic acids from a living body-derived sample" in claims 1 and 2. The terms "level" and "body" are not defined by the claim and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. There is no fixed definition in the art for what constitutes a cellular or intracellular level body. It is unclear, e.g. whether the phrase refers to any body in its entirety, comprising nucleic acids(i.e. an entire animal or plant), or to an isolated sample from just a specific organ/tissue type comprising nucleic acids, to a single cell comprising nucleic acids, an encapsulated mass of nucleic acids or even just to a purified nucleic acid harvested from one of these sources prior to amplification...etc. It is further unclear if the recitation of level is meant to connote an amount of a body(i.e. an increased or decreased level of intracellular body). It is not clear to what other "level" the claim is intended to refer. The claims should be amended to clarify what specific sample types are included in the "cellular or intracellular level body comprising nucleic acids from a living body-derived sample" category. Appropriate correction is suggested.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

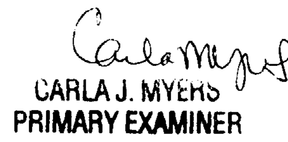
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

4/27/2004

Sally Sakelaris



CARLA J. MYERS
PRIMARY EXAMINER